REMARKS

Following entry of the foregoing amendments, claims 34, 37, 38, 49, 53 to 62, 72, 74 to 78, 94 to 96, and 104 will be pending in this patent application. Claim 38 has been amended herein. No new claims have been added, and no claims have been canceled. Support for the amendments is found throughout the specification as originally filed, and the amendments thus do not introduce new matter into the application.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

Alleged Obviousness

Claims 34, 37, 38, 49, 53 to 62, 72, 74 to 78, 94 to 96, and 104 have been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Elbashir *et al.*, *EMBO Journal*, 2001, 20, 6877-6888 ("the Elbashir article"); published U.S. patent application number U.S. 2003/0143732 ("the Fosnaugh application"); and published U.S. patent application number U.S. 2003/0206887 ("the Morrissey application") in view of the combined teachings of U.S. patent number 6,262,036 ("the Arnold patent"); published U.S. patent application number U.S. 2005/0142535 ("the Damha application"); and U.S. patent number 6,133,246 ("the McKay patent"). Applicants respectfully request reconsideration and withdrawal of this rejection because the claimed compositions would not have been obvious to those of ordinary skill in the art at the time of the invention.

The claims recite compositions comprising two chemically synthesized oligomeric compounds in which at least one of the oligomeric compounds comprises nucleosides having 2'-F substituent groups that alternate with β-D-deoxyribonucleosides. The cited references, when considered individually or in combination, fail to render such compositions *prima facie* obvious.

Because obviousness is necessarily determined as of the time of invention, it is fundamental that the Office avoid using hindsight when assessing obviousness.[1] In this regard, the Supreme Court recently indicated in *KSR Int'l Co. v. Teleflex* that "inventions in

[1] See e.g., *KSR Int'l Co. v. Teleflex*, 127 S.Ct. 1727, (2007) (warning against "the distortion caused by hindsight bias . . . and arguments reliant on *ex post* reasoning."); 35 U.S.C. § 103 (requiring determination of whether an invention "would have been obvious at the time the invention was made.").

most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known."[2] To avoid the trap of hindsight, a finding of obviousness therefore requires the Office to identify "a *reason* that would have prompted a person of ordinary skill in the relevant field to combine the [known] elements *in the way the claimed new invention does*."[3] In applying these principles to a case involving chemical compounds, the Federal Circuit held in *Takeda Chemical Industries, LTD v. Alphapharm Pty, Ltd* that "it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."[4] Moreover, according to the Federal Circuit "an invention would not be deemed obvious if all that was suggested 'was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.'"[5]

In the present case, the Office has failed to provide reasons why those of ordinary skill would have combined particular aspects of the cited references to arrive at the claimed compositions. Instead, the Office relies on hindsight to pick and choose elements from the vast, unpredictable, and in some instances contrary, art to arrive at the claimed subject matter, and the Office has therefore failed to properly establish *prima facie* obviousness. The cited references, in fact, fail to render the claimed compositions obvious, for at least the following reasons.

The Elbashir article describes a total of eight siRNA duplexes in which at least one nucleoside is modified from natural 2'-OH RNA, and all but two of those duplexes are inactive. The tested motifs and results are summarized below:[6]

Motif	**Activity**
Full RNA (control)	Active

[2] *Id.*
[3] *Id.* (emphasis added).
[4] *Takeda Chemical Industries, LTD v. Alphapharm Pty, Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007) (emphasis added).
[5] *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 83 USPQ 2d 1289, 1305 (Fed. Cir. 2007), (citing *In re O'Farrell*, 853F.2d 894, 903 (Fed. Cir. 1988)).
[6] *See Elbashir* at pages 6881-6882 and at Figure 4 at page 6882.

2'-deoxy in two 3' overhangs of each strand	Active
2'-deoxy in four 3' nucleosides (2 overhanging and 2 hybridizing) of each strand	"significantly active"
Full 2'-deoxy in either one or both strands	Inactive
Full 2'-O-Me in either one or both strands	Inactive

The Elbashir article thus describes two active siRNA duplexes comprising 2'-deoxy modifications at the 3'-ends (either the terminal two or four nucleosides) and no active siRNA duplexes comprising 2'-O-methyl substitutions. One skilled in the art cannot determine from the disclosure of the Elbashir article whether, for example, a single 2'-O-methyl substitution anywhere in the duplex is tolerated, because the only 2'-O-methyl-containing duplex was inactive. Further, contrary to the Office's characterization, the Elbashir article does not teach a "correlation between the placement of 2'-substitutions in various places on the oligonucleotides and the retention of siRNAi activity."[7] Rather, the article merely shows that duplexes containing two or four 2'-deoxy modified nucleosides at the 3' end are active and that full 2'-deoxy and full 2'-O-methyl are not, which is far from teaching a correlation between placement of modifications and retention of activity. Based upon the article's teachings, one cannot conclude that placement of the 2'-deoxy modified-nucleosides affects activity. For example, the data support the conclusion that four 2'-deoxy substitutions are tolerated, regardless of position, but some greater number of 2'-deoxy substitutions result in inactivity. Indeed, the authors speculate that "[m]ore extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly." No further guidance regarding number, placement, or type of modifications is provided by the Elabashir article.

The Fosnaugh and Morrissey applications share a common inventor and assignee, and include substantially overlapping text. For convenience, their disclosures will therefore be discussed together, with the differences between them being noted. The Office remarks that both the Fosnaugh and Morrissey applications teach "various ways of designing and

[7] Office action dated December 8, 2008, page 5.

optimizing configurations of 2'-O-modifications on siRNA."[8] The Office overreaches in characterizing these references, however. The applications do not teach ways of designing and optimizing such configurations, but instead describe vast genuses of siRNA molecules and broadly discuss possible chemical modifications for the molecules. In addition to this broad description, the applications describe a number of specific, active siRNA molecules, none of which has a motif of chemical modifications similar to those claimed. Moreover, beyond repeating the observation of the Elbashir article that 2'-deoxy modifications at the 3' end are tolerated, the Fosnaugh and Morrissey applications add virtually nothing to the understanding that the position of the modifications is important.

Specifically, the Fosnaugh application begins with broad generalized teachings, including description of a vast genus of possible nucleoside modifications. For example, page 5 depicts the structure of the ribose sugar ring of a ribonucleoside in which each position (labeled R3, R4, R5, R6, R7, R8, R10, R11, and R12) may independently be modified with any of a list of possible substituents. Although certain 2'-modifications, including 2'-O-methyl, 2'-deoxy, and 2'-fluoro are specifically mentioned, the Fosnaugh application also describes countless modifications at every other possible position of the nucleoside.

The Fosnaugh application continues, discussing the possible numbers of modified nucleosides and/or modified linkages in an oligonucleotide (e.g., about 1 to about 10 or more).[9] Notably absent is mention of an siRNA molecule in which each of the nucleosides of one or both strands is modified. In fact, the Fosnaugh application describes siRNA molecules wherein "one or both strand of the siRNA comprise ribonucleotides at positions within the siRNA that are critical for siRNA mediated RNAi in a cell. All other positions within the siRNA can include chemically modified nucleosides."[10] The Fosnaugh application thus teaches that some unmodified RNA nucleosides are necessary for RNAi activity. Similar discussion is found in the Morrissey application.[11] Significantly, the Fosnaugh and Morrissey applications provide no guidance as to which positions might be "critical for siRNA mediated RNAi."

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[8] Office Action dated December 8, 2008 at page 12.
[9] See page 7.
[10] Fosnaugh at page 9, paragraph 0069.
[11] See page 13, paragraph 0099.

Beyond general statements that do no more than suggest varying all parameters (except for the unidentified "critical" ones), the Fosnaugh and Morrissey applications describe certain specific siRNA molecules. None of the specific molecules comprises a motif of alternating modifications, however. Moreover, the Fosnaugh and Morrissey applications describe a synthesis strategy that involves modifying each nucleoside of a particular base type; that is, each pyrimidine or purine has the same modification, or no modification, throughout the oligonucleotide. As a result, each adenosine of a particular oligonucleotide will have the same modification throughout the oligonucleotide, as will each cytosine, etc. Consequently, the pattern of modifications depends entirely upon the base sequence of the particular oligonucleotide. This sequence-dependent substitution scheme teaches by implication that the pattern or placement of modifications within an siRNA molecule is not critical. Rather, the Fonsaugh application suggests that what matters is the *base sequence* of the oligonucleotide and the types of modifications. Thus, not only do the Fosnaugh and Morrissey applications fail to teach alternating motifs, they do not discuss other motifs or even the concept of motifs. Instead, the pattern of modifications is a matter of chance, dictated by the nucleobase sequence of a particular oligonucleotide.

The Office asserts that the combination of the three primary references (the Elbashir article and the Fosnaugh and Morrissey applications) teach "the importance of routinely testing the placements and types of modifications on siRNA, and the effects of these modifications and their locations on the siRNA molecule on oligonucleotide stability, target binding and the inhibitory capabilities of siRNA."[12] Actually, the combined references describe a vast number of possible modifications at any position of the ribose ring of a ribonucleoside; that certain numbers of some nucleoside modifications within the strands of an siRNA molecule are tolerated; that certain other combinations, such as full 2'-deoxy and full 2'-O-methyl in either or both strands of an siRNA molecule abolishes activity; that two or four 2'-deoxy at the 3'-ends of both strands is tolerated, and that some unmodified RNA at some unidentified positions appear to be necessary or "critical" for retaining activity. This collection of information falls far short of teaching "ways of designing and optimizing configurations of 2'-O-modifications on siRNA," as represented by the Office.[13]

[12] Office Action dated December 8, 2008 at pages 10 to 11.
[13] *Id.* at page 12.

The combination of primary references also describes some of the goals of modified siRNA molecules. For example, the Elbashir article notes that "2'-deoxy modifications may reduce costs of RNA synthesis and may enhance RNase resistance."[14] The Fosnaugh and Morrissey applications aspire to use modifications to "overcome potential limitation of in vivo stability and bioavailability inherent to native RNA molecules . . . enable a lower dose of a particular nucleic acid molecule for a given therapeutic effect . . . longer half-life in serum . . improving cellular uptake . . . minimize the possibility of activating interferon activity."[15] These disclosures do not suggest more definite solutions to achieve these goals, and certainly do not suggest the presently claimed motifs. Significantly, the references do not teach how to balance such objectives in designing an siRNA molecule when, for example, a particular motif or modification improves the molecule with respect to one goal, but diminishes it with respect to another competing goal. The full 2'O-methyl compounds described in the Elbashir article, for example, likely have improved stability and affinity for a target RNA, but they are reported to have no activity, thus making them unsuitable for reducing a target messenger RNA.

The Office attempts to fill the substantial gaps left by the three primary references by relying on three secondary references. Each of these references describes RNase H-dependent antisense compounds, however. RNase H is an enzyme that cleaves the RNA strand of a DNA/RNA duplex. Accordingly, antisense oligonucleotides that reduce a target RNA in a cell by relying on RNase H activity must mimic a DNA strand. Such compounds were known at the time of the present invention to have certain structural requirements. For example, RNase H-dependent antisense oligonucleotides must have a stretch of DNA (2'-deoxy) or DNA-like nucleosides. Particular modifications described in the cited references were known to improve certain properties of RNase H-dependent antisense compounds, provided that the fundamental requirement of DNA or DNA-like nucleosides was preserved. For example, one motif described in the secondary references is a "gapmer," which comprises a central region of DNA nucleosides flanked by regions of modified nucleosides.

The Elbashir article and the Fosnaugh and Morrissey applications describe oligonucleotides suitable for cleaving a target RNA through RNA interference (RNAi). Not

[14] Page 6885.
[15] Fosnaugh at paragraph 0035; Morrissey at paragraph 0052.

surprisingly, the structural requirements for utilizing this mechanism differ from that utilized by RNase H. The active compounds described in the Elbashir article and the Fosnaugh and Morrissey applications are double-stranded RNA compounds comprising at least some unmodified RNA nucleosides. These compounds do not have a region of DNA or DNA-like nucleosides, because such region is unnecessary and would not activate RNAi. Likewise, the secondary references that describe oligonucleotides utilized in RNase H-dependent mechanisms do not include double-stranded RNA-containing compounds such as those described in the Elbashir article and the Fosnaugh and Morrissey applications. The two mechanisms are sufficiently different that there would have been no reason to believe that the modifications or motifs useful for one would have been useful in the other. If one skilled in the art were to have nevertheless looked to the motifs useful for RNase H-dependent mechanisms, such as DNA-containing gapmers, and were to have tried them in RNAi, one would have chosen compounds that failed to activate RNAi (and are not the subject of the present invention).

By teaching motifs that succeed and fail in RNase H-based methods, the secondary references do teach, however, that identifying active motifs is critical for understanding and exploiting biological mechanisms. Those of ordinary skill would have recognized that identifying active motifs for RNAi would require exploiting the requirements dictated by the RNAi mechanism, but that motifs of chemical modifications useful for activating RNase H provide no useful guidance.

With respect to the description provided in each of the secondary references, the Arnold patent describes certain chemically modified oligonucleotides used as RNase H-based antisense molecules. Specifically, the Arnold patent includes substantial description of modified internucleoside linkages, and remarks that such modified linkages may be used in combination with other modifications, including sugar modifications such as 2'-sugar modifications. Indeed, the Arnold patent describes certain oligonucleotides that have both modified linkages and 2'-sugar modifications, and Example 34 of the patent describes antisense oligonucleotides having alternating linkage modifications and uniform 2'-modifications.[16] Although the described oligonucleotides may be useful for RNase H-based

[16] See Col. 49 (noting that "where 2'-deoxy or 2'-O-methyl substitutions are indicated below, these structures occur on all of the residues in the alternating or repeated sequence.").

antisense methods, nothing in the Arnold patent suggests that those oligonucleotides or modifications would be useful in siRNA molecules.

The Damha application describes incorporation of arabinonucleosides, including 2' arabino fluoro nucleosides (FANA), into RNase H-based antisense oligonucleotides. FANA, as described in Damha is "DNA-like" in its conformation.[17] The Damha application thus teaches that oligonucleotides comprising DNA and FANA, which are uniformly DNA-like, support RNase H activity. Significantly, the Damha application lacks any teaching that would be useful in designing siRNA compounds.

The McKay patent describes a vast number of chemical modifications useful for RNase H-based antisense oligonuelcotides. The McKay patent further teaches that such modifications can be arranged in many different motifs, some of which result in compounds capable of effecting RNase H-based reduction of target mRNA. Reported motifs include gapmers, wingmers, hemimers, and fully modified oligonucleotides. The McKay patent does not describe alternating motifs, and teaches nothing about what motifs might be important for siRNA activity. The McKay patent shows the importance of identifying not only useful modifications, but also arranging those modifications in patterns that allow for desired activity.

Nothing in the cited references teaches the claimed compositions comprising first and second oligomeric compounds having 2'-F substituent groups that alternate with β-D-deoxyribonucleosides. Further, none of the references teaches similar motifs or even the fundamental concept that the motif or pattern of modifications is a useful way to approach designing siRNA. As discussed above, the Elbashir article and the Fosnaugh and Morrissey applications describe a few siRNA motifs. The Elbashir article describes the testing of fully 2'-modified siRNAs and indicates that they were inactive. The article further indicates that two to four 2'-deoxynucleotides were tolerated at the 3' ends of siRNAs. The Fosnaugh and Morrissey applications generically discuss varying the number of modified nucleosides in an siRNA, but do not describe the locations for the modified nucleosides. In fact, by linking modification to nucleobase type, the Fosnaugh and Morrissey applications suggest that the pattern of modifications is not important. Certainly, a pattern of alternating modifications is

[17] See e.g., page 15.

not taught. Moreover, the Elbashir article and the Fosnaugh and Morrissey applications all teach that some unmodified RNA nucleosides are necessary for activity. The present claims recite siRNA molecules in which each nucleoside of the antisense and/or sense strand is modified, a nucleoside having a β-D-deoxyribonucleoside being a modified nucleoside due to the lack of oxygen at the 2' position, which is normally present in the nucleosides of RNA molecules. Thus, the oligomeric compounds recited in the present claims lack the "critical" unmodified RNA described in the Fosnaugh application. Not a single *active* compound described in the Elbashir article and the Fosnaugh and Morrissey applications is fully modified. And the only compounds that are fully modified (i.e., have no natural 2'OH RNA nucleosides) were *inactive*. The combined teachings of the Elbashir article and the Fosnaugh and Morrissey applications do not suggest siRNA molecules having a strand of alternating 2'-modifications and actually teach away from compounds that lack any unmodified RNA nucleosides.

The three additional references relied upon by the Office describe modifications and motifs present in molecules used as substrates for RNase H. RNase H requires a single-stranded compound comprising a stretch of DNA or DNA-like nucleosides. The Office fails to provide a sufficient reason why one of skill in the art would have combined references discussing methods that rely upon RNase H activity with references describing siRNAs. Instead, the Office glosses over the difference remarking that "one of ordinary skill in the art would have been motivated to combine the teachings of Elbashir et al Fosnaugh et al and Morrissey et al, as applied to modifying and testing the activity of siRNA, with the teaching by McKay, Damha and Arnold, regarding the incorporation of modifications into inhibitory oligonucleotides, for enhancing their ability to bind a target gene and for their ability to enhance oligonucleotide stability, and design the motifs instantly claimed including alternating 2'-β-D-deoxynucleosides with 2'-modified nucleosides."[18] The Office trivializes the important differences in the biological mechanisms and thus the structural requirements for exploiting those differences.

As noted above, oligonucleotides that are substrates for RNase H are single-stranded and comprise at least four contiguous DNA or DNA-like nucleosides. The Elbashir article

[18] Office Action dated December 8, 2008 at page 8.

teaches that using full DNA in either or both strands of an siRNA molecule results in total inactivity. The only motif described in the cited art that has alternating nucleosides is found in the Damha application and it comprises alternating DNA (2'-deoxy) and F-arabino (FANA) nucleosides. In the context of RNase H oligonucleosides, 2'-deoxy nucleosides are unmodified, so in reality, the Damha application describes alternating FANA and unmodified deoxynucleosides. Further, FANA nucleosides are similar in conformation to DNA, so the compounds described in the Damha application are actually uniformly DNA-like in character. Such compounds could not have been successfully used in an siRNA duplex, as they are expected to have characteristics similar to DNA, which were shown by the Elbashir article to be inactive in the RNAi pathway.

There would have been no reason for one of skill in the art to have combined the teachings from references describing these different mechanisms. Moreover, the claimed compositions are unsuitable for decreasing a target nucleic acid through traditional RNase H mediated mechanisms. The cited references thus fail to teach or suggest the claimed compositions comprising first and second oligomeric compounds having 2'-F substituent groups that alternate with β-D-deoxyribonucleosides and those skilled in the art would have had no reason to design and produce such compositions before Applicants' invention.

Furthermore, the art of siRNA design at the time of the invention was unpredictable. Since those of ordinary skill could not have anticipated which motifs of chemical modifications in siRNA duplexes would have resulted in active compounds, the invention represents a selection from among a vast number of unpredictable possible choices and is therefore non-obvious. It appears that the Office's solution to the vast teaching in the art regarding chemical modification of nucleosides would be to simply to try all possible combinations of modifications. Not only is such an approach impossible, given the vast number of combinations of modifications, it also fails to support an obviousness rejection because the art does not support a finding that the claims represent a selection of a predictable solution.

In *KSR*, the Supreme Court noted that when "there are a *finite* number of identified *predictable* solutions a person of ordinary skill has good reason to pursue the known options

in his or her technical grasp."[19] *KSR* involved simple technology with only a few variables; a control pedal and an electronic throttle, each of which was separately known in the art. In *Takeda*, though, the inventors selected a lead compound from among several hundred for modification and further investigation. In finding non-obviousness, the *Takeda* Court contrasted this situation from that in *KSR*, remarking that, "[r]ather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation."[20] Similarly, the invention in *Ortho McNeil Pharmaceuticals v. Mylan Laboratories,* an epilepsy drug, did "not present a finite (and small in the context of the art) number of options easily traversed to show obviousness."[21]

In *KSR*, once the claimed control pedal was designed, there was little doubt that it would work for its intended purpose. Thus, as the Court noted, the invention was selected from among "predictable solutions." In *Takeda*, though, the lead compound (as discussed above, selected from several hundred) was modified in two ways with unpredictable results. To arrive at the claimed compound from the identified lead, a methyl group was homologated, and the resulting ethyl group was moved from one position on a ring to another. Although these are routine modifications, the court found nothing in the art to predict that "performing the specific steps of replacing the methyl group of the 6-methyl compound with an ethyl group, and moving that substituent to the 5-postion of the ring, would have provided a broad safety margin."[22] Until the compound was made and tested, its properties could not have been predicted. Similarly, the invention in *Sanofi-Synthelabo v. Apotex* was an isolated enantiomer of a known racemate, about which an expert testified that "no known scientific principle allows prediction of the degree to which stereoisomers will exhibit different levels of therapeutic activity and toxicity."[23] Accordingly, the Federal Circuit upheld a finding of non-obviousness, noting that "a person of ordinary skill in this

[19] *KSR* at 1742 (emphasis added).
[20] *Takeda* at 1359.
[21] 520 F.3d 1358, 1364 (Fed. Cir. 2008).
[22] *Id.*
[23] 550 F.3d 1075, 1087 (Fed. Cir. 2008 .

field would not reasonably have predicted that the dextrorotory enantiomer would provide all of the antiplatelet activity and none of the adverse neurotoxicty."[24]

The issue in the present case is thus whether the selected combination of modifications utilized in the claimed compositions would have been predictable (like the simple electronic control throttle in *KSR*) or unpredictable (like the chemical modifications in *Takeda* or the enantiomers in *Sanofi-Synthlabo*). The Office has offered no reason why those skilled in the art would have predicted that such a selection would yield active siRNA compounds. Instead, the Office relies on evidence that some nucleoside modifications can provide benefits when used in different motifs in a different mechanism: RNase H. Not only is such reliance illogical, it would likely have led to the selection of the wrong molecules. For example, even if one skilled in the art could have safely assumed that the nucleoside modifications useful in RNase H substrates would provide similar benefits in siRNA molecules, one still must have determined where to place those modifications within the siRNA molecules. For RNase H substrates, a commonly used motif is a 'gapmer,' which comprises modified nucleosides in terminal wings flanking a central region of deoxynucleosides.[25] Compounds comprising such a gapmer motif with deoxynucleoside gaps are unsuitable for siRNA molecules, however, and are not claimed. The Office does not explain how one of skill in the art was to know which portions of the art to use and which portions to reject when designing siRNA compounds.

In addition, the references cited by the Office discuss some of the complicating and often competing goals for siRNA molecules.[26] The Office dismisses the complexity of siRNA design by simply remarking that certain modifications can provide desirable properties and apparently concluding that all motifs therefore would have been obvious. Omitted from that conclusion is the complicated, unpredictable reality that improving any one property may reduce or abolish another property. For example, the full 2'-O-methyl compounds described in the Elbashir article would have been expected to have desirable resistance to nucleases and to have high affinity for target messenger RNA. The Elbashir article reports, however, that such compounds were totally inactive, making them unsuitable

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[24] *Id.*
[25] See e.g., McKay, Col. 11, lines 32 to 64 and Tables 11, 12, 14, 19, 21, 24, and 26.
[26] See for example Fosnough at paragraph 0035 (discussing the competing desirability of improving stability, bioavailability, and activity).

as siRNA molecules. Many variables influence whether siRNA molecules bearing particular motifs of modifications will be active. In the setting of such unpredictability, the Office provides no reasonable basis for selecting the particular motifs recited in the present claims. The Office glosses over this complexity, blithely labeling it "optimization" or "design choice." In reality, balancing competing properties has proven to be unpredictable and extremely challenging.

Furthermore, the cited references describe inactive compounds. The Office improperly relies on the description of active compounds to suggest that siRNA design is predictable, while ignoring the inactive compounds. "It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggest to one of ordinary skill in the art."[27] If active compounds suggest that other compounds sharing certain modifications will likewise be active, then inactive compounds having those same modifications must suggest the opposite. When "prior art contains apparently conflicting references, the [Patent Office] must weigh each reference for its power to suggest solutions to an artisan of ordinary skill."[28] When one considers the state of the art on balance, it becomes clear that the modifications described in the cited references are neither universally beneficial nor detrimental. Rather, the art teaches that modifications may provide benefits or detriments depending upon their number and placement within an oligonucleotide. As in *Takdea* and *Sanofi*, at the time of filing, there was no known scientific principle to allow prediction of which motifs would be active and which would not. Such level of unpredictability in the art is incompatible with a finding of obviousness.

In light of the unpredictability in the art at the time of the invention, and the fact that the Office has failed to provide credible reasons why those skilled in the art would have designed and produced oligomeric compound bearing the claimed pattern of chemical modifications before applicants' invention, compositions comprising the compounds would

[27] *In re Wesslau* 53 C.C.P.A. 746, 750 (1965); see also *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448 (Fed. Cir. 1986) (holding that the district court improperly ignored portions of a reference that led away from obviousness).
[28] *In re Young* 927 F.2d 588, 591(Fed Cir. 1991).

not have been obvious at that time. Applicants accordingly, respectfully, request withdrawal of the rejection.

Alleged Double Patenting

Claims 34, 37, 38, 49, 53 to 62, 72, 74 to 78, 94 to 96, and 104 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 36, 44, 46 to 49, 52 to 64, 74 to 80, 93, 98 to 100, and 106 of copending U.S. patent application number 10/860,265. Claims 34, 37, 38, 49, 53 to 62, 72, 74 to 78, 94 to 96, and 104 have also been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 35 to 63 of copending U.S. patent application number 11/054,848. Applicants request deferral of these rejections pending the identification of allowable subject matter in the present application, as the rejections can likely be readily resolved, depending upon the subject matter ultimately allowed, through the filing of suitable terminal disclaimers.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the official action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,

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/Jane E. Inglese/
Jane E. Inglese, Ph.D.
Registration No. 48,444

Woodcock Washburn LLP
Cira Centre
2929 Arch Street, 12th Floor
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439